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Carcinogenic Activity of Acrylamide in the Skin and Lung of Swiss-ICR Mice

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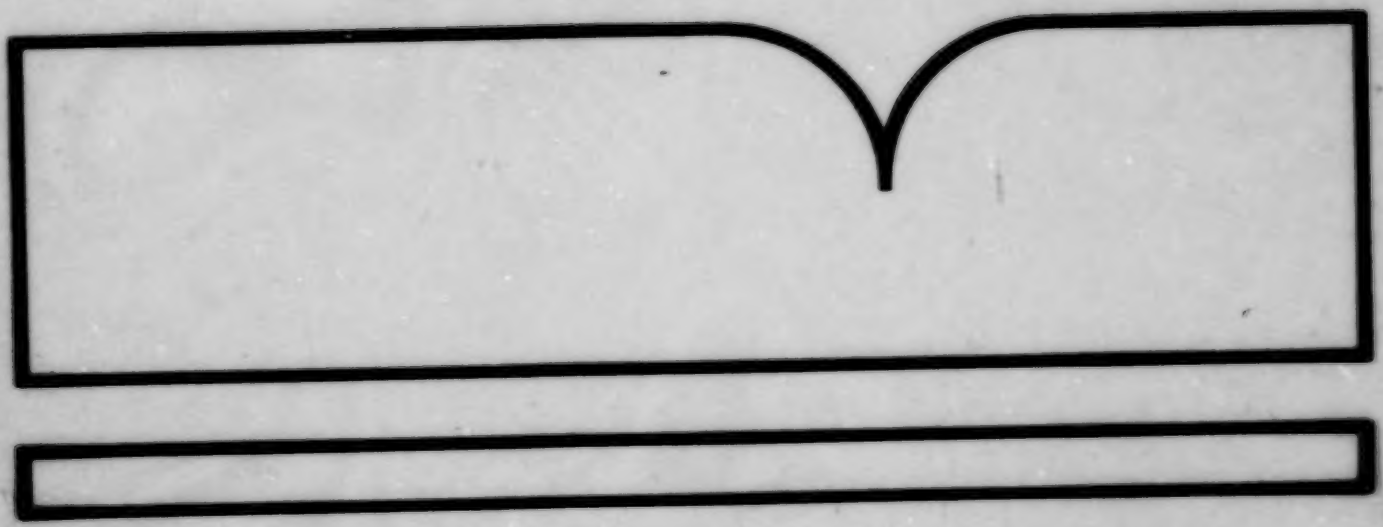

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16. ABSTRACT

Doses of acrylamide ranging from 12.5 to 50 mg/kg were administered orally to female ICR-Swiss mice over a M, W & F for two weeks (total doses of 75, 150 and 300 mg/kg). Two weeks later some of the animals were begun on a promotion schedule involving the application of 2.5 µg TPA/mouse three time weekly. Development of tumors was observed weekly in the skin and in the lungs at one year. Acrylamide was found to initiate squamous cell adenoma and carcinomas in the skin and increased the yield of adenomas and carcinomas in the lung. Skin tumor development was dependent upon TPA promotion whereas lung tumor induction was not. These data extend previous observations of carcinogenic activity of acrylamide in the skin Sencar mice and lungs of strain A/J mice to a third strain of mouse the ICR-Swiss.

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CARCINOGENIC ACTIVITY OF ACRYLAMIDE IN THE SKIN AND LUNG OF SWISS-ICR MICE

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SUMMARY

Doses of acrylamide ranging from 12.5 to 50 mg/kg were administered orally to female ICR-Swiss mice over 3 days for each of 2 weeks (total doses of 75, 150 and 300 mg/kg). Two weeks later some of the animals were started on a promotion schedule involving the application of 2.5 μg TPA/mouse 3 times weekly. Development of tumors was observed weekly in the skin, and in the lungs at 1 year. Acrylamide was found to initiate squamous cell adenoma and carcinomas in the skin and increased the yield of adenomas and carcinomas in the lung. Skin tumor development was dependent upon 12-*O*-tetradecanoylphorbol-13-acetate (TPA) promotion whereas lung tumor induction was not. These data extend previous observations of carcinogenic activity of acrylamide in the skin of SENCAR mice and lungs of strain A/J mice to a third strain of mouse, the ICR-Swiss.

INTRODUCTION

Previous work reported from this laboratory demonstrated that acrylamide was capable of initiating tumors in the skin of SENCAR mice and increased the incidence of lung adenomas in strain A/J mice [1]. These studies were undertaken because of the structural similarity between acrylamide and vinyl carbamate, the postulated proximate carcinogenic form of ethyl carbamate [2]. The present paper reports the extension of this work to a third strain of mouse, the Swiss-ICR.

MATERIALS AND METHODS

Acrylamide was obtained from Eastman Kodak Chemical Co., of Rochester, NY. It was determined to be of greater than 99% purity by coupled gas chromatographic and mass spectral analysis [1]. TPA was obtained from Chemical Carcinogenesis Co, Eden Prairie, MN.

Female Swiss-ICR mice were randomly assigned to 6 groups of 40 animals each. Acrylamide was dissolved in water and administered orally by gavage in doses of 0, 75, 150 and 300 mg/kg divided into 6 equal portions over a 2-week period. Ethyl carbamate served as the positive control and was administered in the same fashion to a total dose of 300 mg/kg. Two weeks after the last dose a promotion schedule was begun consisting of tri-weekly applications of 2.5 μg TPA dissolved in acetone to the shaved back of each mouse for a period of 20 weeks. The sixth group of animals received a total dose of 300 mg acrylamide/kg, administered as described above, but received applications of 0.2 ml acetone to the back in place of TPA. The appearance of papillomas on the shaved back was charted by location on a weekly basis for individual animals. To be included in the cumulative count, a papilloma had to exceed 1 mm in diameter and be present for 3 consecutive chartings. After a total of 52 weeks on study the surviving animals were killed. The observed tumor counts were analyzed for a dose-response using Gehan's multiple comparison test [3]. The skin and lungs of these animals and those which died during the course of the experiment were taken for histological evaluation of all gross lesions. These data were analyzed for significant increases over the control response using Fisher's exact test.

RESULTS

Table 1 provides a summary of skin tumors observed during the study. Acrylamide, when followed by TPA promotion, produced a dose-related increase in the number of animals which bore skin tumors (33% in the high dose group vs. none in the control group). This increase was reflected in an average cumulative yield of 0.43 tumors/animal ($P < 0.01$). In the absence of TPA treatment, only a single skin tumor was observed in 40 animals over the 1-year observation period. Ethyl carbamate treatment followed by TPA promotion produced skin tumors in 10% of the animals with an average yield of 0.13 tumor/animal.

There was also a dose-related increase in the number of squamous cell carcinomas observed in animals which were treated with acrylamide followed by TPA promotion (Table 1). At the highest dose of acrylamide a significant increase ($P = 0.05$) in carcinoma yield was observed in the group receiving TPA promotion. Only 1 carcinoma was observed in the group that did not receive TPA. Three of the 5 tumors observed in animals treated with ethyl carbamate and TPA were carcinomas. The difference between the total tumors observed at autopsy vs. the cumulative yield of tumors was related to the regression of papillomas. In a few cases, moribund animals were lost to cannibalism or autolysis.

The combined yield of alveolar bronchiolar adenomas and carcinomas was increased significantly in a dose-related manner ($P < 0.03$) by acrylamide treatment. This was also observed with the high dose of acrylamide in the absence of TPA promotion ($P < 0.01$). Combination of the 2 groups receiving total doses of 300 mg/kg of acrylamide (1 treated with TPA, the

TABLE 1

TUMOR INITIATING ACTIVITY OF ACRYLAMIDE IN THE SKIN OF FEMALE SWISS ICR MICE

Chemical	Dose[a] (mg/kg)	TPA[b]	Cumulative no. of tumor bearing animals[c]	Cumulative no. tumors/animal	Histological classification of squamous cell tumors at autopsy	
					Papilloma	Carcinoma
Distilled H_2O	0.2 ml	+	0/40 (35)	0	0	0
Acrylamide	75	+	4/40 (34)	0.10	1	1
	150	+	4/40 (32)	0.13	0	3
	300	+	13/40 (32)	0.43	6	4
	300	—	10/40 (36)	0.03	0	1
Ethyl carbamate	300	+	4/40 (33)	0.18	2	3

[a]Dose was administered orally in 6 divided portions over a 2-week period to the total indicated.
[b]TPA was applied at a dose 2.5 μg/mouse in acetone 3× weekly for 20 weeks beginning 2 weeks after the last dose of initiator.
[c]To be included in the cumulative count a 1-mm mass had to be present in the same location for 3 consecutive weekly observations. Numbers of animals begun in each group is indicated as the denominator of the ratio. Animals surviving to termination of the experiment at 1 year included in parentheses.

other without TPA treatment) indicated a highly significant lung response to acrylamide ($P < 0.001$) relative to the control. A fairly high incidence of malignant lymphoma was observed in the lungs of animals included in this experiment (data not shown). However, their incidence has no clear relationship to acrylamide or ethyl carbamate treatments.

TABLE 2

LUNG TUMOR INCIDENCE IN ICR-SWISS MICE TREATED WITH ACRYLAMIDE

Chemical	Dose[a] (mg/kg)	TPA[b]	N[c]	Alveolar bronchiolar		
				Adenoma	Carcinoma	Total
Distilled H_2O	0.2 ml	+	36	3	1	4
Acrylamide	75	+	34	6	2	8
	150	+	36	5	1	6
	300	+	34	10	1	11
	300	—	36	4	10	14
Ethyl carbamate	300	+	36	9	8	17

[a]Dose was administered orally in 6 divided portions over a 2-week period to the total dose indicated.
[b]TPA was applied at a dose 2.5 μg/mouse in acetone 3× weekly for 20 weeks beginning 2 weeks after the last dose of initiator.
[c]*N* = no. of animals available for autopsy without unacceptable levels of autolysis. Each group initially contained 40 animals.

DISCUSSION

It is clear from the present data that acrylamide is capable of acting as a tumor initiator in the skin of Swiss-ICR mice. This result confirms previous observations in the SENCAR mouse [1]. The only notable difference is that the Swiss mice appear to be somewhat less susceptible to acrylamide induced skin tumors than the SENCAR. For example, 75% of SENCAR mice bore papillomas with total dose of 300 mg/kg compared to 43% of the Swiss mice. In addition, carcinoma yields in all 3 doses tested totalled 15 in a population of 120 animals in the SENCAR whereas 8 carcinomas were observed at the same doses and group sizes of Swiss mice. Consequently, the sensitivity of SENCAR mice to acrylamide is approximately 2 times that of the Swiss-ICR. More precise comparison of this compound's relative potency as a tumor initiator by the oral route in these 2 strains is precluded by the neurotoxicity of acrylamide that is observed at total doses exceeding 300 mg/kg.

Increases in lung adenomas and carcinomas in animals receiving acrylamide treatments were consistent with observations previously reported in strain A/J mice [1]. The response rates (total alveolar bronchiolar tumor yield) at the doses utilized displayed a reasonably strong relationship with dose ($P < 0.03$) despite the fact of a relatively low response over background. Observation of even a somewhat greater response in lung tumors in the absence of TPA administration confirms that acrylamide is capable of producing such tumors in the absence of treatment with a second chemical. If this latter group is combined with the group that received TPA promotion but the same dose of acrylamide, it is reasonably clear that acrylamide is capable of inducing malignant tumors in the lung as well as the skin.

In conclusion, the present data further argues that acrylamide should be considered a chemical carcinogen of the same general level of potency as ethyl carbamate [1].

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